

Environmentally Friendly Chemistry with Organophosphorus Syntheses in Focus

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Abstract

The use of the microwave (MW) technique has many advantages in organophosphorus chemistry. MW irradiation may replace a catalyst, or simplify a catalytic system. New reactions may also become possible under MW irradiation. In most cases, microwaves just make the reactions more efficient in respect of rate, selectivity and yield. The benefits are shown via representative examples. In another field, our methods developed for the resolution of cyclic phosphine oxides and phosphinates are summarized. After deoxygenation, the racemic or optically active P-heterocycles were used as P-ligands in platinum complexes that together with other derivatives are potential catalysts. The third topic embraces the optimization of the synthesis of dronic acids/dronates. Starting from the corresponding carboxylic acids and using methanesulfonic acid as the solvent, 3 equivalents of phosphorus trichloride is enough as the P-reactant. Applying sulfolane as the solvent, the optimum set of reactants comprises 2 equivalents of phosphorus trichloride and phosphorous acid.

Keywords

organophosphorus chemistry, green chemistry, microwave, resolution, platinum complexes, dronic acids/dronates

Introduction

In this minireview, our recent results in environmentally-friendly (“green”) chemistry have been summarized. In the first sub-chapter the usefulness of the microwave technique is shown in organophosphorus chemistry. The second sub-chapter summarizes our results on the resolution of cyclic phosphine oxides, as precursors for P-ligands and on the synthesis of platinum complexes as potential catalysts. Catalysts are of utmost importance from the point of view of green chemistry. The last sub-chapter comprises our experiences on the optimization of the synthesis of dronic acid derivatives that are important drugs against bone diseases.

1 Microwave-Assisted Organophosphorus Synthesis

1.1 The Potential of Microwave Irradiation in Synthetic Organic Chemistry

The use of the microwave (MW) technique in organic syntheses spread fast in research laboratories, and after almost three decades it is close to gaining industrial applications [1]. These days, sophisticated MW equipment is available and utilized on a wide scale of syntheses, such as substitutions, acylations, esterifications, alkylations, C–C coupling reactions, additions, eliminations, condensations, cycloadditions, rearrangements and the formation of heterocycles [2].

It is possible that a catalyst can be omitted or simplified under MW conditions. The most valuable benefit is when a reaction can be performed that is impossible on conventional heating. This may be the consequence of a so-called special MW effect [3]. The most common benefits from MW irradiation are the considerable shortening of the reaction times and the increase in the selectivity and yield. In this article, the advantages of the use of the MW technique are demonstrated within the discipline of organophosphorus chemistry. Organophosphorus compounds including P-heterocycles find applications in synthetic organic chemistry as reactants, solvents (ionic liquids), catalysts and P-ligands in catalysts, and, due to their biological activity, also as components of medicines and plant protecting agents [4-6]. The application of the MW technique in organophosphorus chemistry is a relatively new field [7-13].

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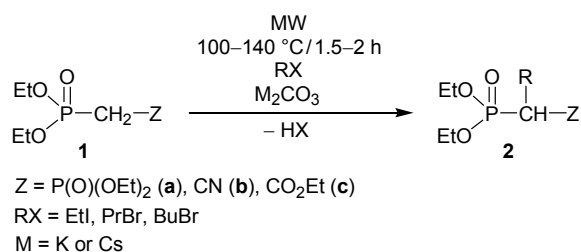
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In this subchapter, the advantages of the application of the MW irradiation are shown via selected examples.

1.2 Reactions in which the Catalysts are Replaced or Simplified by MW Irradiation

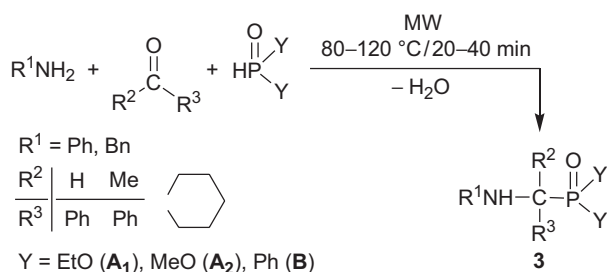
We found that simple CH-acidic compounds underwent a liquid–solid phase C-alkylation by reaction with alkyl halides in the presence of K_2CO_3 under solvent-free MW-assisted conditions. It means that the phase transfer catalyst could be substituted by MW irradiation [14,15]. This method was then extended to the alkylation of tetraethyl methylenebisphosphonate (**1a**), diethyl cyanomethylphosphonate (**1b**) and triethyl phosphonoacetate (**1c**) to afford the corresponding monoalkylated products (**2a–c**) in variable yields (Scheme 1) [16–18].



Scheme 1

The dialkylation of CH-acidic compounds were also elaborated under similar, but more forcing conditions [19].

In another field, valuable α -aminophosphonates (**3A**) [20] and α -aminophosphine oxides (**3B**) were synthesized by the solvent- and catalyst-free MW-assisted Kabachnik–Fields condensation of primary amines, aldehydes/ketones and $>\text{P}(\text{O})\text{H}$ species (Scheme 2) [21]. In earlier syntheses, special catalysts (*e.g.* BiNO_3 [22], phthalocyanine [23], lanthanoid(OTf)₃ [24], magnesium perchlorate [25] and gallium(III) iodide [26]) were applied that cannot be regarded environmentally friendly species. We proved that under MW conditions there was no need for any catalyst. It was also found that the syntheses can be carried out without the use of any solvent [27].

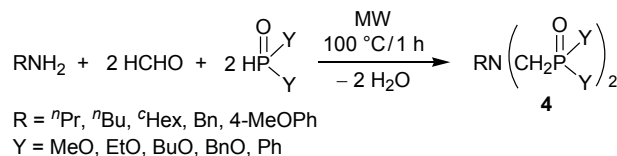


Scheme 2

Applying heterocyclic amines or $>\text{P}(\text{O})\text{H}$ species, the α -aminophosphonates and α -aminophosphine oxides synthesized included *N*-heterocyclic [28] and *P*-heterocyclic derivatives [29].

A few *N*-(2*H*-pyranonyl)- α -aminophosphonates or - α -aminophosphine oxides were also synthesized starting from 3-amino-2*H*-pyran-2-one derivatives [30,31].

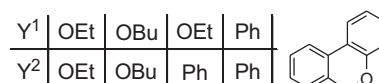
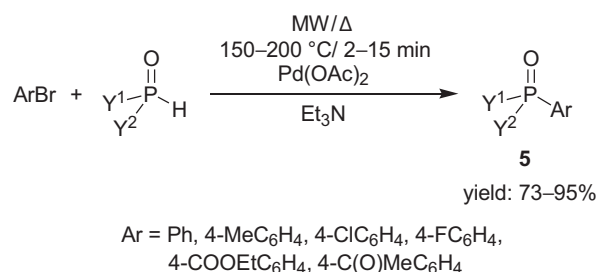
Double “phospha-Mannich” condensations were also developed applying two equivalents of the formaldehyde and the $>\text{P}(\text{O})\text{H}$ species to one equivalent of the primary amine (Scheme 3) [32–34].



Scheme 3

The bis(phosphinoxidomethyl)amines (**4**, $\text{Y} = \text{Ph}$) were useful precursors of bidentate *P*-ligands after double deoxygenation that could be used for the synthesis of ring platinum complexes [32–34]. (More details in Subchapter 2.2)

The Hirao reaction is the coupling of aryl halides and dialkyl phosphites in the presence of $\text{Pd}(\text{PPh}_3)_4$ and triethylamine. Many variations were elaborated in the last two decades [35,36]. It is noteworthy that the Pd-catalyzed reaction took place efficiently in the presence of $\text{Pd}(\text{OAc})_2$ without any ligand on MW irradiation (Scheme 4) [37]. The corresponding products (**5**) were formed in high yields (73–95%). This is the first case for the *P*-ligand-free accomplishment of the Hirao reaction.



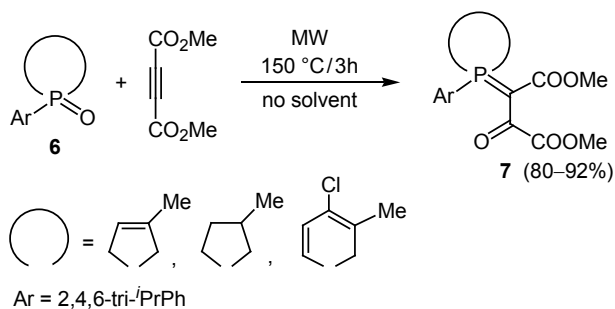
Scheme 4

Arylphosphonates (**5**, $\text{Y}^1 = \text{Y}^2 = \text{alkoxy}$) may also be obtained by the MW-assisted Arbuzov reaction of aryl bromides and trialkyl phosphites [38].

We also found that in the O-alkylation of phenols, the MW irradiation and the phase transfer catalyst synergized each other [39,40]. Quaternary ammonium salts served as special alkylating agents [41]. In the MW-assisted O-alkylation of phosphinic acid, the use of a phase transfer catalyst was useful, when alkyl halides of normal or decreased reactivity were used [42,43].

1.3 Reactions Otherwise Very Slow or Impossible Under Thermal Conditions

The use of the MW technique was useful in the inverse Wittig-type reaction of 2,4,6-triisopropylphenyl-3-phospholene oxides, -phospholane oxides and -1,2- dihydrophosphinine oxides (all marked by **6**) and dimethyl acetylenedicarboxylate to provide β -oxophosphoranes **7**. Completion under thermal conditions required a *ca.* 2 week's heating at 150 °C. At the same time, on MW irradiation, the reaction was complete already after 3 h at the same temperature. No solvent was used in either case (Scheme 5) [44,45].



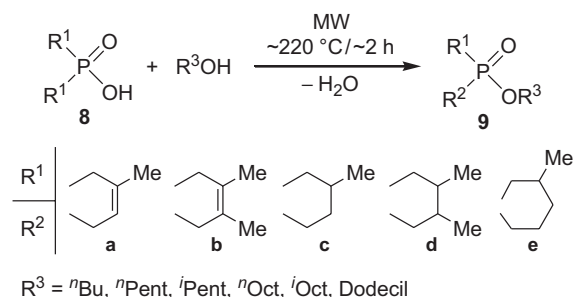
Scheme 5

With 2,4,6-triethylphenyl substituent, the reaction took place only on MW irradiation [44].

It is well-known that phosphinic acids (**8**) do not undergo direct esterification with alcohols to give phosphinates (**9**) (Scheme 6/A). For this, the esters of phosphinic acids (**9**) are usually prepared by the reaction of phosphinic chlorides (**10**) with alcohols in the presence of a base (Scheme 6/B) [4]. Another possibility is the synthesis by the Arbuzov reaction (Scheme 6/C) [4].

The esterification method in use (Scheme 6/B) has the drawback of using relatively expensive *P*-chlorides (*e.g.* **10**). Besides this, the hydrogen chloride formed as the by-product has to be bound by a base. Consequently, the method is not atomic efficient and is not environmentally-friendly.

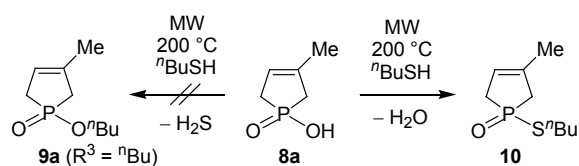
We were successful in the direct esterification of phosphinic acids with alcohols used in a *ca.* 15-fold excess under MW conditions. A series of phosphinic acids underwent efficient esterification using alcohols with longer chain at around 200 °C on MW irradiation (Scheme 7) [43, 46–48].



Scheme 7

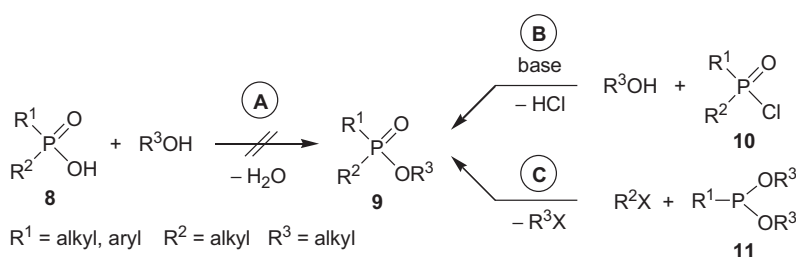
The esterification of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides (**8a** and **8b**), 1-hydroxy-phospholane oxides (**8c** and **8d**) and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxide (**8e**) was carried out in a closed vessel to afford the phosphinates (**9a-e**) in acceptable to excellent yields [43,46–48]. The method elaborated by us is of a more general value. It was also found that the esterification of phosphinic acids is thermoneutral, and controlled kinetically [47].

The esterification of 1-hydroxy-3-methyl-3-phospholene oxide (**8a**) was also attempted with thiobutanol. In this case, the thiobutoxy-phospholene oxide (**10**) was obtained in a yield of 38%. No butoxy-product **9a** ($R^3 = n\text{Bu}$) was formed (Scheme 8) [49].



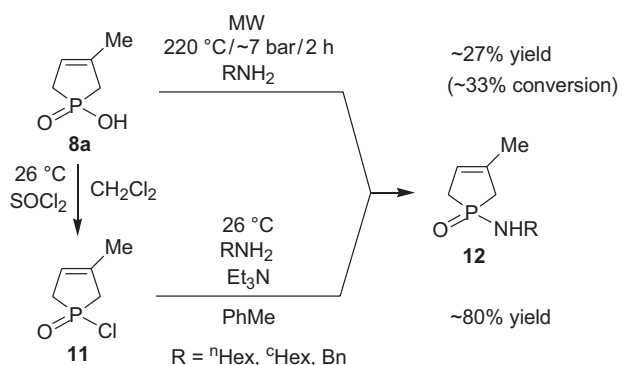
Scheme 8

The outcome of the reaction confirmed that indeed the alcohol is phosphinoylated and that the phosphinic acid is not alkylated. The conversion was, however, moderate which was in accord with the results of the quantum chemical calculations. It was found that the thioesterification is rather endothermic (48.5 kJ mol⁻¹), and the enthalpy of activation is higher (145 kJ mol⁻¹), than that for the reaction with butanol (102 kJ mol⁻¹) [49]. Hence, the incomplete conversion even under MW conditions is justified.



Scheme 6

It seemed to be also interesting to attempt the MW-assisted direct amidations of 1-hydroxy-3-methyl-3-phospholene oxide (**8a**). Using hexylamines and benzylamine at 220 °C, the amidations took place in rather low (*ca.* 33%) conversions [50]. We had to return to the old method synthesizing the cyclic phosphinic amides (**12**) via the corresponding phosphinic chloride (**11**) as the intermediate. In this way, the amides (**12**) were obtained in yields of *ca.* 80% (Scheme 9) [51].

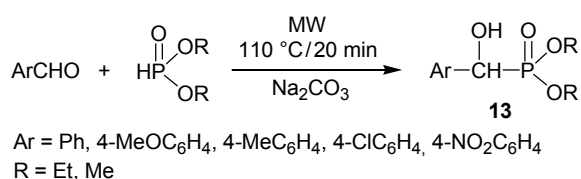


Scheme 9

1.4 Reactions that Became More Efficient Under MW Conditions

There are a lot of reactions within organophosphorus chemistry that became more efficient on MW irradiation [7]. The advantages include faster and more selective reactions. Besides this, in most of the cases, there is no need for solvents. Such reactions include, for example, Diels–Alder cycloadditions [52], fragmentation-related phosphorylations [53] and Arbuzov reactions as shown above in Subchapter 1.2 [38].

The MW-assisted synthesis of α -hydroxyphosphonates (**13**) from substituted arylaldehydes and dialkyl phosphites under solventless conditions may be another example (Scheme 10) [54].



Scheme 10

In another variation, the dialkyl phosphites were added onto the carbonyl group of α -ketophosphonates (**14**). In the reaction of acetylphosphonates (**14**, $\text{R}^1 = \text{Me}$), the target hydroxy-methylenebisphosphonates (**15**) were obtained selectively under MW conditions. However, in the reaction of benzoylphosphonates (**14**, $\text{R}^1 = \text{Ph}$), the formation of mixed phosphonates–phosphates (**16**) was inevitable as a result of a rearrangement (Scheme 11) [55,56].

The hydroxy-methylenebisphosphonates are analogues of dronic acids/dronates which are used widely in the treatment of bone diseases [57]. See Subchapter 3.

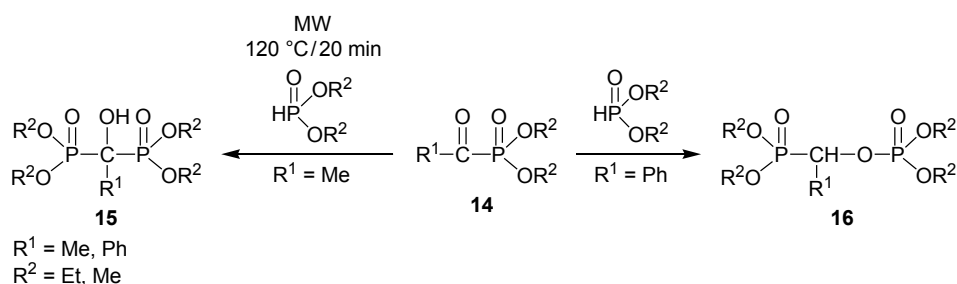
In summary, the MW technique was shown to have an increasing potential in organophosphorus chemistry. In certain instances, MW irradiation may substitute catalysts. In other cases, it may make possible otherwise impossible transformations, or, as in most cases, simply promotes the reactions.

2 The Resolution of Cyclic Phosphine Oxides and the Synthesis of Platinum-Phosphine Complexes

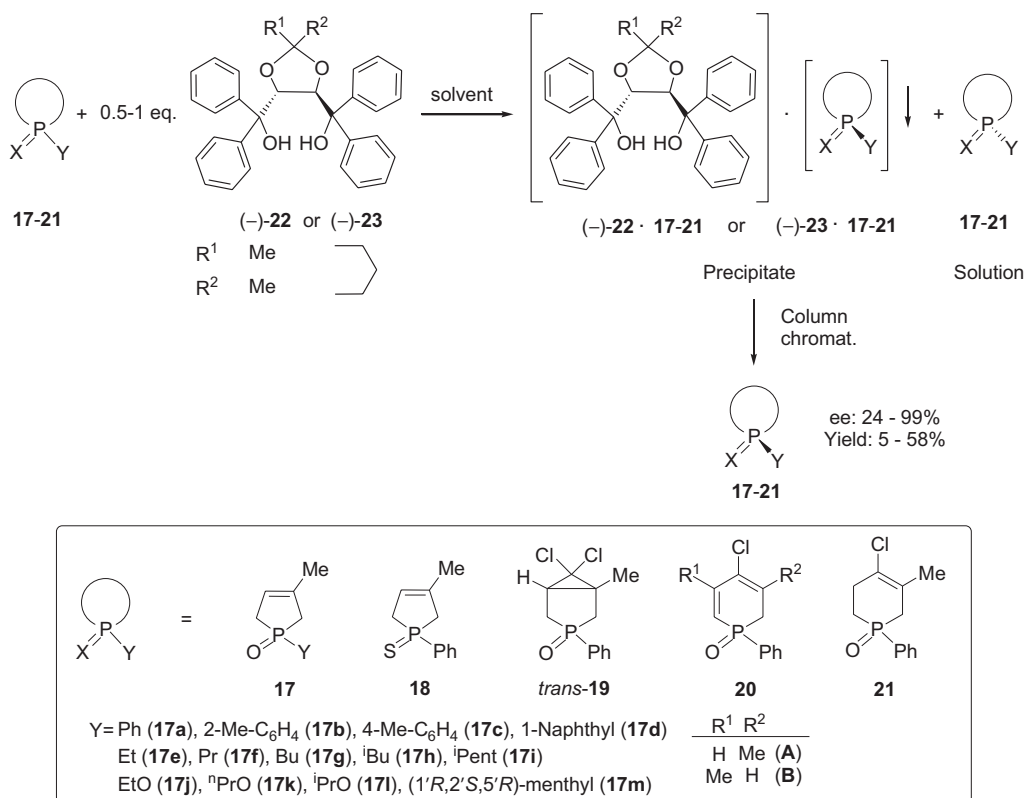
2.1 Resolution of the Optical Isomers of Cyclic Phosphine Oxides

The preparation of *P*-chiral phosphines in enantiopure form is of great interest, as the transition metal complexes of these P(III)-ligands may be applied as enantioselective catalysts in various homogeneous catalytic reactions. A well-established route for the preparation of the optically active *P*-chiral phosphines is the resolution of the racemic phosphine oxides followed by deoxygenation taking place, in most of the cases, by retention [58,59].

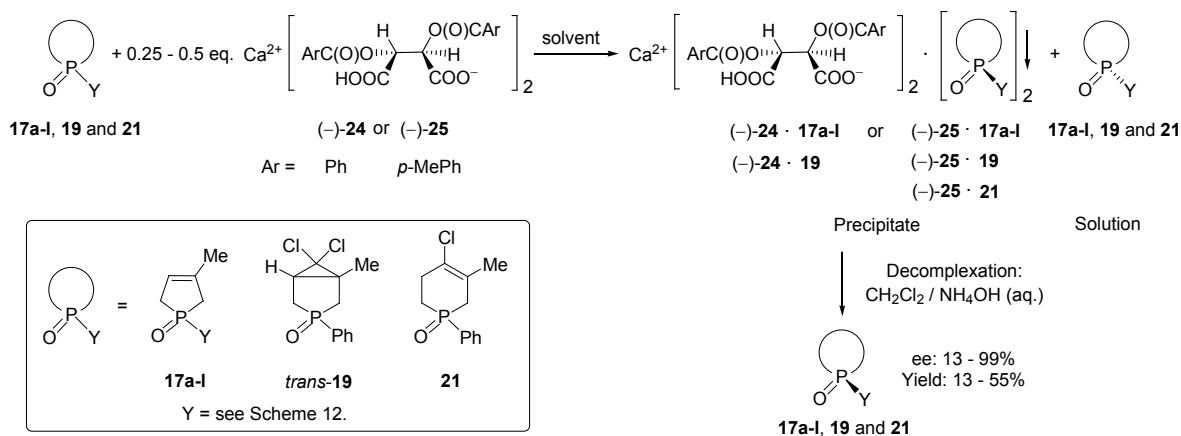
In recent years, efficient resolution methods for 5- and 6-membered *P*-heterocycles, such as 1-aryl-, 1-alkyl- and 1-alkoxy-3-phospholene oxides (**17**), 1-phenyl-3-phospholene sulfide (**18**), 3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**19**), 1-phenyl-1,2-dihydrophosphinine oxide (**20**) and 1-phenyl-1,2,3,6-tetrahydrophosphinine oxide (**21**) were elaborated in our research group using TADDOL derivatives (**22** and **23**) [60–66], as well as the Ca^{2+} salts of *O,O'*-dibenzoyl- and *O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (**24** and **25**) as resolving agents [67–75]. The resolution of the 5- and 6-membered *P*-heterocycles (**17–21**) was possible using TADDOL derivatives (**22** and **23**) via the formation of diastereomeric molecular complexes.



Scheme 11



Scheme 12



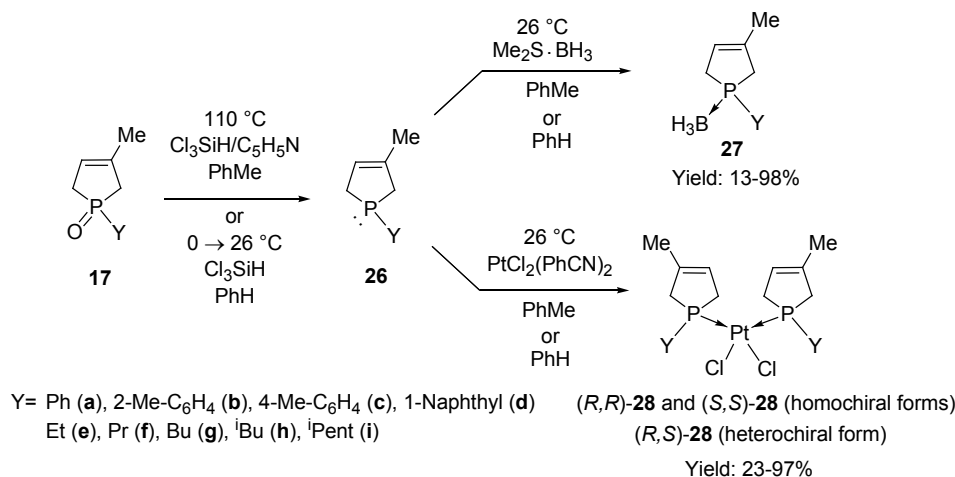
Scheme 13

The diastereomers were purified by recrystallizations, and the *P*-heterocycles (**17-21**) were recovered by column chromatography (Scheme 12) [60-66,70-75]. In most instances, the resolutions were carried out in a mixture of ethyl acetate and hexane [60,61], but alcohols were also suitable solvents [63,73-75]. Moreover, the replacement of ethyl acetate by other solvents influenced the efficiency of the resolutions, as well as the nature of the enantiomer incorporated in the diastereomer formed during the resolution of 3-phospholene oxides (**17**). This phenomenon allowed us to develop resolution procedures for both enantiomers of the 3-phospholene oxides (**17**) from the racemic compounds [63,74,75].

Besides the TADDOL derivatives, the acidic Ca²⁺ salts of *O,O'*-dibenzoyl- and *O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (**24-25**) were also suitable resolving agents for the separation

of the enantiomers of 3-phospholene oxides (**17**), 3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**19**), and 1-phenyl-1,2,3,6-tetrahydrophosphinine oxide (**21**). In these cases, the separation of the enantiomers was accomplished via the formation of diastereomeric coordination complexes (Scheme 13). The diastereomers obtained were purified by digestion (*i.e.* by stirring the crystalline diastereomers at the appropriate temperature in the given solvent), and the enantiomers or enantiomeric mixtures of the 5- or 6-membered *P*-heterocycles (**17a-l**, **19** or **21**) were recovered by treating the dichloromethane solution of the diastereomeric coordination complexes with aqueous ammonia [67-69,71-75].

The neutral Ca²⁺ salts of *O,O'*-dibenzoyl- and *O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid, as well as the acidic and neutral Mg²⁺ salts of the *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid could



Scheme 14

also be applied as resolving agents for the separation of the enantiomers of 3-phospholene oxides (**17**). However, in these cases, the success was limited [68,69,74,75].

The above mentioned resolution methods applying TADDOL- and tartaric acid derivatives (**22-25**) may be regarded efficient as, almost in all instances, at least one of the resolving agents (**22-25**) provided the enantiomers of the 5- and 6-membered *P*-heterocycles (**17-21**) with an *ee* above 99%.

The absolute *P*-configurations of the enantiomers of the 3-phospholene oxides (**17**) were determined by X-ray crystallography and CD spectroscopy [60,61,67,69,74-76]. Crystals suitable for X-ray were obtained in the presence of the corresponding resolving agents (**22-25**) that gave insights into the interactions between the host and guest molecules, and made possible a better understanding of the phenomenon of the molecular recognition.

2.2 Complexation Reactions of Cyclic Phosphines and Bisphosphines

P-heterocyclic derivatives are of interest among the P(III)-compounds that are used as ligands in transition metal complexes applied as catalysts in homogeneous catalytic reactions. In the last years, the synthesis and catalytic activity of a variety of transition metal complexes incorporating mono- or bidentate 5-, 6- or 7-membered *P*-heterocycles were described [77]. Our research group also studied the synthesis of the platinum complexes with *P*-heterocyclic and bisphosphine ligands [78,79]. Many of them were tested as catalysts in the hydroformylation of styrene. In many instances, the borane complexes of the corresponding *P*-heterocycles that may be regarded as the precursors of phosphines, were also synthesized. The phosphines may be liberated from the borane complexes by reaction with secondary amines (*e.g.* diethylamine) [80].

The 1-aryl- and 1-alkyl-3-phospholene oxides (**17a-i**) were subjected to deoxygenation by trichlorosilane or with a mixture of trichlorosilane and pyridine, and the 3-phospholenes (**26**)

so obtained were reacted with borane-dimethylsulfide or dichlorodibenzonitrile platinum(II) to afford the corresponding borane- or platinum complexes (**27** or **28**), respectively. The characteristic ¹*J*_{Pt-P} couplings in the ³¹P NMR spectra confirmed that the platinum complexes (**28**) incorporating the phospholene moieties in position *cis* were formed exclusively (Scheme 14) [66,73,78,81,82].

The optically active aryl- and alkyl-3-phospholene oxides ((*R*)- or (*S*)-**17a-i**) obtained by resolution with TADDOL- or tartaric acid derivatives (**22-25**) were also converted to the corresponding optically active borane- and *cis*-platinum complexes (**27*** or **28***) (Fig. 1). It is known that the deoxygenation with trichlorosilane or with a mixture of trichlorosilane and pyridine takes place with retention of the *P*-asymmetric center, so the enantiomeric excess of the optically active borane- and platinum complexes (**27*** or **28***) was the same, as that in the corresponding starting materials, 3-phospholene oxides ((*R*)- or (*S*)-**17a-i**). The stereostructures of the optically active 3-phospholene platinum complexes (**28***) were evaluated by high-level quantum chemical methods [66,73,78,81,82].

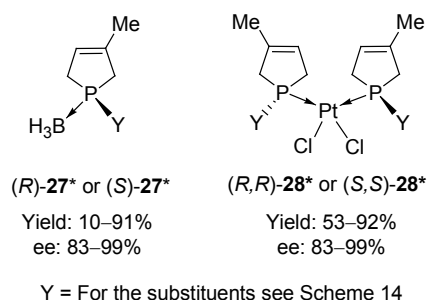
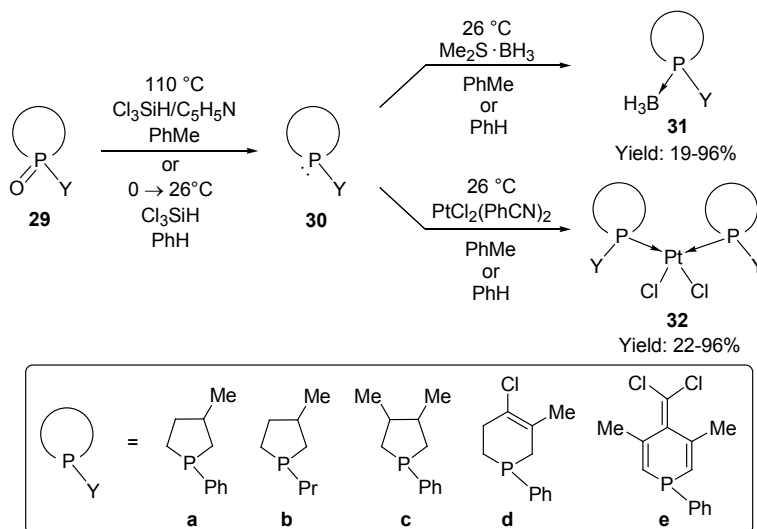


Fig. 1 The optically active 3-phospholene-borane- and 3-phospholene-platinum complexes prepared (**27*** and **28***)

Similarly to the 3-phospholene oxides (**17a-i**), the racemic phenyl- and propyl-phospholane oxides (**29a-c**), the 5-methyl-4-chloro-1,2,3,6-tetrahydroposphine oxide (**29d**) and the 4-dichloromethylene-3,5-dimethyl-1-phenyl-



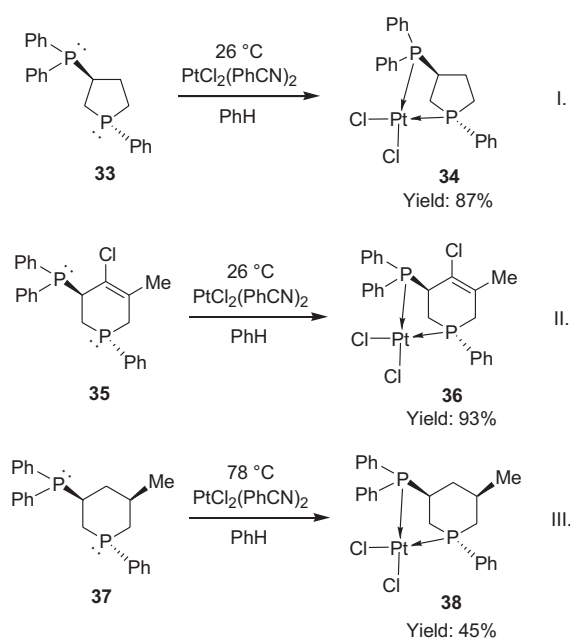
Scheme 15

1,4-dihydrophosphinine oxide (**29e**) were also converted to the corresponding borane- and *cis*-platinum complexes (**31** and **32**) (Scheme 15) [66,78,81].

Recently, our research group investigated and rationalized the possibilities for the deoxygenation of 5-membered *P*-heterocycles, such as phenylphospholene oxides and phenylphospholane oxides (e.g. **17a** and **29a**) using silanes including the traditional and the more user friendly Cl_3SiH , PhSiH_3 , tetramethyldisiloxane and polymethylhydrosiloxane [83].

Bidentate *P*-heterocyclic ligands having exocyclic PPh_2 -functions, such as the 3-diphenylphosphino-1-phenylphospholane (**33**), the 3-diphenylphosphino-1-phenyl-1,2,3,6-tetrahydrophosphinine (**35**) and the 3-diphenylphosphino-1-phenyl-1,2,3,4,5,6-hexahydrophosphinine (**37**) were converted to the corresponding *cis*-platinum complexes (**34**, **36** and **38**), respectively, after double deoxygenation of the corresponding oxides by trichlorosilane (Scheme 16). The relative position of the two P(III)-functions was confirmed by ^{31}P NMR spectral data and quantum chemical calculations [65, 84–88]. It is noteworthy, that the platinum complex of the 3-diphenylphosphino-1-phenyl-1,2,3,6-tetrahydrophosphinine (**36***) was also prepared in an optically active form [65].

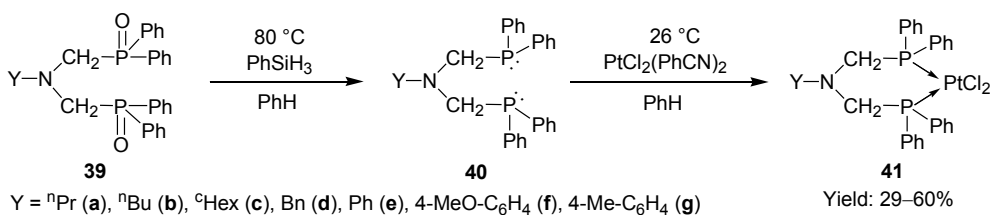
Several bis(phosphinoxidomethyl)amines (**39**) obtained by the double Kabachnik-Fields reaction (see Subchapter 1.2) of the corresponding amine, two equivalents of paraformaldehyde and two equivalents of $\text{Ph}_2\text{P(O)H}$ were subjected to double deoxygenation using phenylsilane. The reaction of bisphosphines (**40**) so obtained with dichlorodibenzonitrile



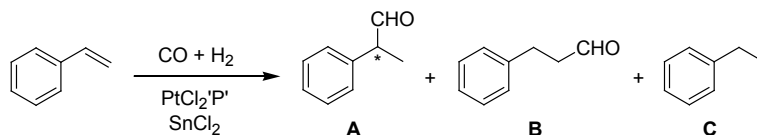
Scheme 16

platinum(II) afforded the corresponding *cis*-platinum complexes (**41**) (Scheme 17). The structure of the platinum complexes **41a**, **41c** and **41f**, as well as the intermolecular interactions were investigated by quantum chemical calculations, and X-ray crystallography [33,34,89].

The platinum complexes of the mono- or bidentate *P*-heterocyclic ligands (**28**, **32b-c**, **34**, **36**, **38**, **41c-d** and **41f-g**) were tested as catalysts in the hydroformylation of styrene (Scheme 18) [34,66,73,82,84,90]. The selectivity of the catalyst is important, as



Scheme 17



Scheme 18

branched and linear aldehyde (**A** and **B**), as well as ethylbenzene (**C**) can be formed in this reaction (Scheme 18).

In most of the cases, an unusual preference for the branched aldehyde was observed that makes our Pt-complexes valuable.

3 The Synthesis of Dronic Acids/Dronates

3.1 Optimization of the Synthesis of Dronic Acids/Dronates

1-Substituted-1-hydroxy-1,1-methylenebisphosphonic acid derivatives (dronic acids or dronates) can be used against various bone diseases. Fig. 2 shows *geminal*-bisphosphonates (**42**) and the pyrophosphate analogues (**43**). The methylene-function of bisphosphonates presents a basis for tailoring the biological and physiological properties through the appendage of R¹ and R² side-chains. In dronic acids and dronates, the R¹ group represents a hydroxy substituent. The resulting 1-hydroxy-1,1-bisphosphonate arrangement provides a tridentate functionality towards binding Ca²⁺ ions, and hence promotes the affinity for species responsible for the accumulation of phosphates in the bone tissues [57].

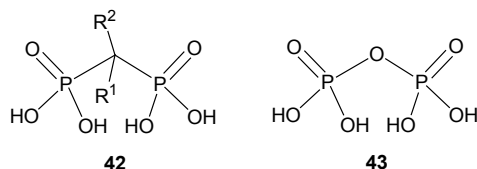


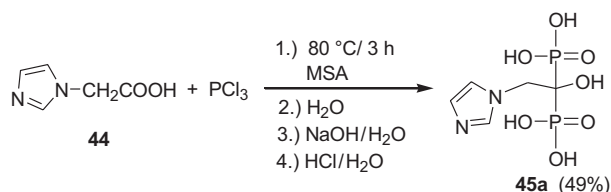
Fig. 2 General structures of bisphosphonates and pyrophosphates

The practical synthesis of dronic acids involves the three-component reaction of a substituted carboxylic acid, phosphorous acid and a *P*-chloride, which is usually phosphorus trichloride, and rarely phosphorus oxychloride. The molar ratio of the components applied varied on a broad scale and the solvents applied embrace a wide spectrum including aromatics (chlorobenzene and toluene), 1,4-dioxane, 1,2-dimethoxyethane, PEG-400, n-octane, sulfolane, methanesulfonic acid (MSA) [57].

Regarding the synthesis of zoledronic acid (**44**), the ratio of imidazolylacetic acid, phosphorous acid and phosphorus trichloride varies significantly as reflected by the 1:1–5:2–4.6 combinations reported. The yields provided are rather variable and move on a broad scale of 24–86%. With lack of purity criteria, the yields may refer to crude mixtures consisting mainly of the dronic acid and its monosodium salt. In the literature, the ratio and the excess of the *P*-reactants has never been explained or commented on. In most cases, inadequate

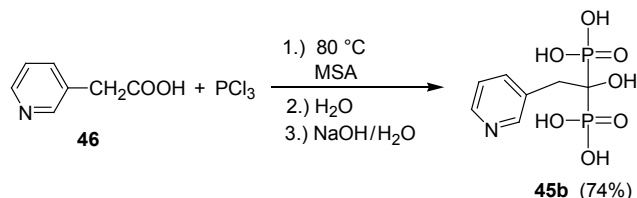
ratios and unnecessary excesses were used in the unoptimized reactions. This resulted in a ‘black-box’ in respect of the synthesis of dronic acids/dronates. Moreover, a large quantity of hydrochloric acid is formed by hydrolysis of the excess phosphorus trichloride. We were the first who studied, the synthesis of zoledronic and risedronic acids in detail to establish the optimum choice and ratio of the reactants. In addition, we wished to obtain insights into the reaction sequence for the formation of hydroxy-methylenebisphosphonic acids [91].

First, the reaction of imidazolylacetic acid (**44**), phosphorous acid and phosphorus trichloride leading to zoledronic acid (**45a**) was studied in MSA at 80 °C (Scheme 19) [91]. The optimal set of parameters comprised the use of only phosphorus trichloride as the P(III) species in a quantity of 3.2 equivalents. After completion of the reaction (3 h), the mixture was hydrolyzed, neutralized and the crude product containing the mixture of zoledronic acid (**45a**) and its monosodium salt (**45a-Na**) was recrystallized from aqueous hydrochloric acid to afford pure zoledronic acid (**45a**) in a yield of 49% in a purity of 98%.



Scheme 19

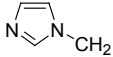
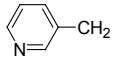
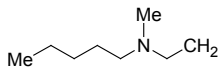
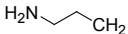

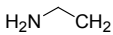
Similar experiments were carried out for the synthesis of risedronic acid (**45b**) applying pyridylacetic acid (**46**) and phosphorus trichloride (Scheme 20.) [91]. In this case, there was no need for a recrystallization at the end. The use of 3.1 equivalents of phosphorus trichloride (again in the absence of phosphorous acid) led to a yield of 74% of risedronic acid **45b**.



Scheme 20

From the above experiments, it is clear that under the conditions applied there is no need to use phosphorous acid in the preparation of dronic acids. At the same time, efficient syntheses require the presence of 3.2 equivalents of phosphorus trichloride. This may mean that phosphorous acid may have

Table 1 Rational synthesis of dronic acids/dronates

$ \begin{array}{c} \text{R}-\text{C}(=\text{O})\text{OH} \\ \xrightarrow[3.) \text{NaOH/H}_2\text{O}]{\begin{array}{l} 1.) 3.2 \text{ equiv. PCl}_3 \\ 75-85^\circ\text{C}/3-24 \text{ h} \\ \text{MSA} \\ 2.) 105^\circ\text{C}/4 \text{ h} \\ \text{H}_2\text{O} \end{array}} \\ \text{45a-g} \end{array} $						
Dronate (45)	R	X	Y	Hydrate	Purity (%)	Yield (%)
zoledronic acid (a)		H	Na→H	–	100	49
risedronic acid (b)		H	H	1×H ₂ O	100	74
ibandronate (c)		H	Na	–	98	46
alendronate (d)		H	Na	3×H ₂ O	98	57
etidronate (e)	Me	Na	Na	–	90	36
fenidronate (f)		Na	Na	–	100	42
pamidronate (g)		H	Na	2×H ₂ O	97	51

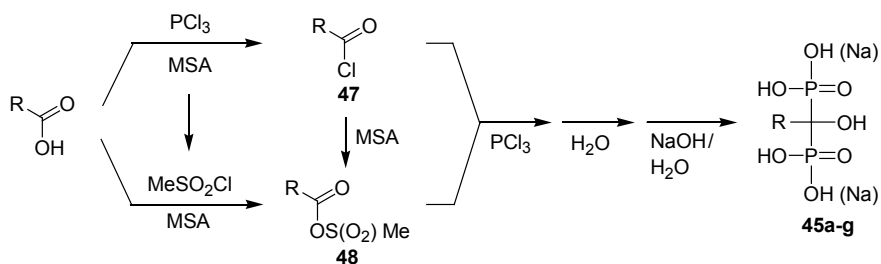
been applied in vain in earlier dronic acid syntheses, and quantities of phosphorus trichloride beyond 3.2 equivalents were unnecessary. The unjustified use of phosphorous acid and the unnecessary excess of phosphorus trichloride results in extra costs and environmental burdens (after the excess phosphorus trichloride was hydrolyzed) [91,92]. On the other hand, when phosphorus trichloride was used in a quantity less than 3 equivalents, the conversions were incomplete causing again extra costs in the production of dronic acids/dronates.

Based on the above reactions, we also elaborated the synthesis of ibandronate (**45c**) and alendronate (**45d**) [93]. Etidronate (**45e**) [94], fenidronate (**45f**) [95] and pamidronate (**45g**) [96] were also prepared in this way. The experimental data are summarized in Table 1. It can be seen, that in certain cases the acid, while in the other instances the monoNa salt, or the diNa salt were formed.

3.2 Mechanistic Considerations on the Formation of Dronic Acids/Dronates

A possible route for the formation of dronic acids in the reaction of a carboxylic acid with phosphorus trichloride in MSA is shown in Scheme 21. Our idea is that 1 equivalent of the phosphorus trichloride is needed to convert the acid to the corresponding acid chloride (**47**). In MSA as the solvent, a mixed anhydride $\text{RC(O)O(O)}_2\text{SMe}$ (**48**) may also be formed from the acid chloride and a molecule of solvent, or in another way. In the second step, the intermediates (acid chloride **47** and anhydride **48**) formed are reacted further with the remaining part of the phosphorus trichloride, a step that is followed by hydrolysis and pH adjustment (Scheme 21) [97].

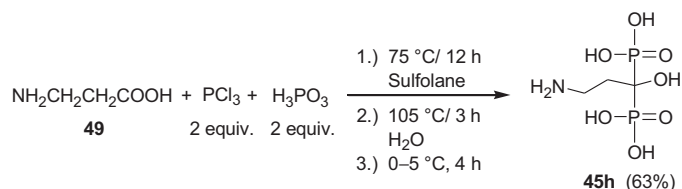
When sulfolane was used as the solvent in the synthesis of pamidronic acid from β -alanine (**49**) instead of MSA, no



for R, see at Table 1.

Scheme 21

product was formed, if phosphorus trichloride or phosphorous acid was used alone as *P*-reagent. We had to use phosphorus trichloride and phosphorous acid together in the reaction. The optimal ratio was 2 equivalents of phosphorous acid and 2 equivalents of phosphorus trichloride. In this case, pamidronic acid (**45h**) was crystallized after the hydrolysis in a yield of 63%, and in a purity of 100% (Scheme 22) [96].



Scheme 22

The use of sulfolane as the solvent in the synthesis of other dronic acid/dronates and the mechanism of these reactions are under study. We also investigated the possibility of applying other *P*-reactants.

In summary our minireview may have provided an overview on at least three aspects of “green” chemistry performed in our laboratory, on MW-assisted organophosphorus chemistry, on the synthesis of *P*-ligands and Pt-complexes incorporating them to form potential catalysts, and in the field of optimizing the synthesis of dronic derivatives.

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